PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing (*day/month/year*) 16 MAY 2005
Applicant's or agent's file reference 021216000810	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/34386	18 October 2004 (18.10.2004)	17 October 2003 (17.10.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): G01N 33/53,33/533,33/534,33/547,21/176; C07F 9/32; C07K 16/00 and US Cl.: 435/7.1,7.5; 436/172,545,546; 530/389.8; 558/202

Applicant

INTEGRIGEN, INC.

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Shafiqul Haq Telephone No. 703-308-0198

Form PCT/ISA/237 (cover sheet) (January 2004)

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims NONE	YES
	Claims 1-10	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-48	NO
Industrial applicability (IA)	Claims 1-48	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

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Supplemental Box
In case **the space in any of the preceding boxes is not sufficient.**

V. 2. Citations and Explanations:

(1) Claims 1-10 lack novelty under PCT Article 33(2) as being anticipated by Patricelli et al. (US 2003/0175986 A1).

The present claims relate to detection of proteolytic antibody using halogen phosphonate monoester probes.

The cited reference discloses methods and composition for detecting/analyzing complex protein mixtures (especially enzymes e.g hydrolases) (paragraph 0037) using activity based probes (halegen phosphate monoester) (Abstract and Fig.1).

The referenced probes (Fig 1 and claim 12) anticipate halogen phosphonate monoester probe of claim 1 wherein X=halogen; R^2= unsubstituted alkyl; L^1=substituted alkylene and R^1= detectable label.

Patricelli et al. disclose a method comprising contacting complex proteins with halogen phosponate monoester probe and detecting the active target protein bound with labeled halogen phosphonate monoester (page 19, claim 1 and page 20 claims 12-14).

Patricelli et al. do not disclose proteolytic antibody but detection of proteolytic antibody (antibody having enzymatic activity) is inherent in the method of detection of enzymes (e.g serine hydrolases) (paragraph 0037) as protein samples (paragraph 0025) would also include proteolytic antibodies with catalytic traid arrangement of subfamily of serine proteases.

Therefore, the reference is deemed to anticipate the cited claims.

(2) Claims 1-10 lack novelty under PCT Article 33(2) as being anticipated by Liu et al. (PNAS, 1999).

Claims recite detection of proteolytic antibody using halogen phosphonate monoester probes.

The cited reference discloses a method and for detection of serine hydrolases using activity based probes (halogen phosphate monoester) (Title and Abstract).

Liu et al. disclose activity based probes (page 14694, Scheme 1) that anticipate halogen phosphonate monoester probe of claim 1 wherein X=halogen; R^2= unsubstituted alkyl; L^1=substituted alkylene and R^1= detectable label.

Liu et al. disclose a method which comprises contacting proteins with halogen phosponate monoester probe and detecting the active target protein bound with labeled halogen phosphonate monoester (page 14695, right column, lines 24-60).

Liu et al. do not disclose proteolytic antibody but detection of proteolytic antibody (antibody having enzymatic activity) is inherent in the method of detection of serine hydrolases as protein samples would also include proteolytic antibodies with catalytic traid arrangement of subfamily of serine proteases.

Therefore, the reference is deemed to anticipate the cited claims.

(3) Claims 11-19 and 38-48 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraphs (1) and further in view of Paul et al. (J. Biol. Chem. 2001).

Patricelli et al. disclose halogen phosphonate monoester probe as discussed above but fail to disclose conjugation of the halogen phosphate monoester probe with affinity tag (e.g. biotin) for immobilization.

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Supplemental Box
In case **the space in any of the preceding boxes is not sufficient.**

Paul et al. in a method of detection of proteolytic antibody using phosphonate ester probes disclose using affinity tag (e.g. biotin) (page 28315, fig.1 and page 28316, left column, lines 49-53).

Therefore, it would have been obvious at the time of the invention to a person of ordinary skill in the art to include affinity tags as taught by Paul et al. in the halogen phosphonate monoester probe of Patricelli et al. to obtain equivalent halogen phosponate monoester probe useful for affinity separation or for immobilization to solid support containing immobilizing moiety (e.g. avidin).

(4) Claims 20-37 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the preceding paragraph (1) and further in view of Paul et al. (US 6,235,714 B1).

Patricelli et al. disclose halogen phosphonate monoester probe as discussed above but fail to disclose conjugation of the halogen phosphate monoester probe with antigen to produce proteolytic antibody as claimed (claim 22 wherein X=antigen).

Paul et al. in a method of identifying inducers of proteolytic antibody using phosphonate monoester probes disclose using antigen-halogen monophosphate conjugate (column 8, lines 15-21, 44-45)

Therefore, it would have been obvious at the time of the invention to a person of ordinary skill in the art to attach an antigen tag as taught by Paul et al. in the halogen phosphonate monoester probe of Patricelli et al. to obtain halogen phosponate monoester probe useful for production of proteolytic antibody.

(5) Claims 1-48 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.